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(72) Inventors EBERHARD HOFMANN and ULRICH HOLTSCHMIDT

(54) BIOCIDAL PREPARATION

(71) We, TH. GOLDSCHMIDT A.G., a body corporate organised under the Laws of Germany, of 100 Goldschmidtstrasse, 43 Essen, Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to biocidal mixtures.

Synergistic biocidal mixtures have previously been proposed in which one of the components of the mixture is a quaternary ammonium compound. Moore and Hardwich in "Manufacturing Chemist", Volume 27 (1956), page 308, have suggested synergistic mixtures of quaternary ammonium compounds and phenols. The synergism is, however, not very pronounced and occurs solely below the critical Micelle-concentration.

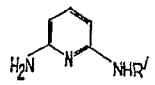
These suggested mixtures exert pronounced irritation on skin and eyes and are therefore not suitable from a practical point of view.

Synergistic preparations containing quaternary ammonium compounds and non-ionic tensides have also been disclosed in the Specification of U.S. Patent No. 3,223,643. These latter synergistic preparations, it is true, represent an improvement considered from the bacteriological point of view but they have important drawbacks which limit their practical application. Thus, the previously proposed synergistic preparations possess pronounced toxicity as well as sensitivity, i.e. loss of activitiy, in the presence of protein, lipids and anionic detergents, such as soaps, alkylsulphates and alkylsulphonates. For all these reasons, the usefulness of these preparations is exceedingly limited.

According to the present invention there is provided a biocidal mixture, comprising

(a) a quaternary ammonium compound and

(b) a 2 - N - alkyl(or aralkyl)amino - 6-aminopyridine of the general formula



wherein R' is an alkyl radical containing 8 to 18 carbon atoms, the number of carbon atoms being even, or a benzyl radical which is chlorinated or brominated in 2- and/or 4-position, the weight ratio of (a):(b) being from 1:5 to 5:1.

Aminopyridines of the above-mentioned formula have been described and claimed, for example, in the Specification of our copending Patent Application No. 7621 of 1970 (Serial No. 1256983).

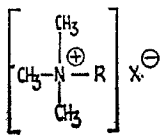
Preferably the present mixture additionally contains, (c) a non-ionic tenside, in which event the weight ratio between components (a), (b) and (c) should be from 1:5:10 to 5:1:0.1.

The present mixtures are eminently suitable as the effective component of biocidal preparations, e.g. aqueous solutions, dispersions or solids.

It is particularly surprising that the bacteriological effect of the present mixtures is greater than that of the individual components of the mixture. The bacteriological effect of the present mixture as compared with that of the individual components is particularly superior in the acidic pH-range. It is also unexpected and certainly could not be predicted that the present mixtures are substantially unaffected by protein and soaps while at the same time exhibiting a significantly reduced irritation effect on the skin including the mucous membranes.

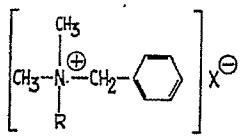
The following three principal representations of quaternary ammonium compounds are particularly suitable for the present purposes, although others may be used:—

a)



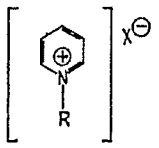
wherein R is an alkyl radical containing 8 to 18 carbon atoms and X stands for a halogen atom, or an OH or CH_3OSO_3 group,

b)



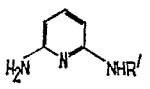
wherein R is an alkyl radical containing 8 to 18 carbon atoms, and X stands for a halogen atom, or an OH or CH_3OSO_3 group, and

c)

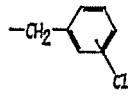


wherein R is an alkyl radical containing 8 to 18 carbon atoms and X stands for a halogen atom, or an OH or CH_3OSO_3 group.

Of the 2 - N - alkylamino - 6 - aminopyridines, the compounds disclosed in the Specification of our copending Patent Application No. 7621 of 1970 (Serial No. 1256983) of the following general formula are particularly suitable:



In this formula, R′ stands for an alkyl radical containing 8 to 18 carbon atoms, the number of carbon atoms being even, or benzyl which is chlorinated or brominated in the 2- and/or 4-position. In a preferred embodiment R′ is an alkyl radical containing 8 to 12 carbon atoms or a radical of the formula:



For the purpose of obtaining a preparation which may also be used for cleaning purposes or which is capable of foaming, it is recommended to add to the mixture or the preparation a non-ionic tenside. Suitable tensides or surface active agents for this purpose are the addition products of ethylene oxide to a number of compounds, such as, for example, synthetic C_8—C_{18}-alcohols prepared from natural carboxylic acids, higher alkylated phenols, such as isooctyl-, nonyl- or dodecylphenol, fatty acid glycerinol- or sorbitol esters as well as mixed polymers of ethylene- and propylene oxide and oxyethylation products of higher fatty acid amides, such as stearic- and lauric acid oxyethylamides. The bacteriological effect of the present mixtures is not substantially affected by the addition of such non-ionic tensides. Accordingly, the synergism takes place between the quaternary ammonium compound and the 2 - N - alkylamino - 6 - aminopyridine, but not between the ammonium compound and the non-ionic tenside.

The preparation of the present mixtures is effected in exceedingly simple manner by mere mixing of the individual components at a temperature of from 0 to 100° C. The individual components may be mixed *per se* or in the form of a solution or dispersion in water, an alcohol, such as methanol, ethanol, propanol, ethyleneglycol and propyleneglycol, or a glycoether, such as dioxane, dimethylglycol or diglycol. If an acidic pH-value is desired, the mixing may be effected in the presence of an organic or inorganic acid, such as acetic acid, citric acid, lactic acid, hydrochloric acid or phosphoric acid. By contrast, an alkaline pH-value can be obtained by adding, for example, sodium hydroxide, sodium carbonate, sodium phosphate (Na_3PO_4) or triethanolamine.

With the view to obtaining satisfactory skin compatibility, it is, however, advantageous, if the pH of the preparation does not exceed a value of 9.

Depending on the nature of any solvent or carrier vehicle employed in making the present mixture, the mixture may be obtained in the form of a liquid preparation, a stable dispersion or as a solid of solid consistency. The present preparations may be used, for example, as disinfectants and preservatives in food stuffs, such as milk, meat or other protein containing foods, and find general application in food processing plants as well as hospitals, animal breeding establishments and breweries. The present preparations are also effective algaecides. The present preparations in liquid form may be prepared in any desirable concentration, preferably fairly concentrated, and be diluted with water or solvent as desired for use. The preparations may, for example, be diluted to the extent that the concentration of the active ingredient is from 0.001 to 0.1 percent by weight.

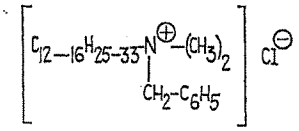
The invention will now be described by several examples of biocidal mixtures and their preparation, it being understood, however, that these examples are given by way of illustration and not by way of limitation:—

EXAMPLE 1

A clear homogeneous solution was obtained by mixing with stirring at about 50° C.

100 parts by weight of 2 - octylamino - 6-aminopyridine,
200 parts by weight of solution A,
200 parts by weight of N - propanol,
20 parts by weight of concentrated acetic acid,
10 parts by weight of sodium acetate, and
270 parts by weight of water.

Solution A contained 50% by weight of the compound



40% of water and 10% of ethyl alcohol. The chain length of the above mentioned compound was composed of 50% of alkyl radicals of 14 carbon atoms, 40% of alkyl radicals of 12 carbon atoms, and 10% of alkyl radicals of 16 carbon atoms.

The homogeneous clear solution thus obtained contained 25% by weight of bactericidally active component and could be diluted with water in any desired ratio.

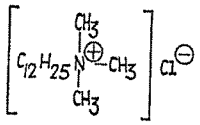
EXAMPLE 2

100 parts by weight of 2 - dodecyl - amino-6 - aminopyridine,
200 parts by weight of solution A,
200 parts by weight of an addition product of 12 mol ethyleneoxide to 1 mol tridecylalcohol,
30 parts by weight of concentrated acetic acid,
10 parts by weight of sodium acetate,
100 parts by weight of ethyl alcohol, and
360 parts by weight of water

were homogenized by agitation at a temperature of 40° C. A clear foaming solution containing 20% of bactericidally active component was obtained. The solution could be diluted with water to any desired extent.

EXAMPLE 3

100 parts by weight of 2 - octylamino - 6-aminopyridine,
500 parts by weight of a solution containing 80% of



and 20% of ethanol,
300 parts by weight of ethanol, and
100 parts by weight of water

were homogenized at 50° C. with stirring. A clear solution containing 50% of bactericidally active component was obtained. The solution could be diluted with water in any desired ratio.

EXAMPLE 4

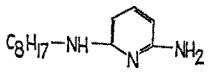
100 parts by weight of 2 - octylamino - 6-aminopyridine,
50 parts by weight of N - cetylpyridiniumbromide,
100 parts by weight of an addition product of 15 mole ethyleneoxide to nonylphenol,
30 parts by weight of concentrated acetic acid,
10 parts by weight of sodium acetate,
200 parts by weight of ethylglycol, and
110 parts by weight of water

were homogenized at a temperature of 30° C. with stirring. A clear solution containing 25% of bactericidally active component was obtained which could be diluted with water in any desired ratio.

The excellent bacteriological activity of the present preparations, as compared to the bacteriological effect of the starting compounds is demonstrated in the following bacteriological test Tables. The test method employed was the so called suspension test according to the "Richtlinien der Deutschen Gesellschaft fuer Hygiene und Mikrobiologie" (guidelines of the German society for hygiene and microbiology).

I. *Bacteriological effect of*:

a) present mixture of



(1 part by weight) and quaternary ammonium compound of the above composition of Example 4 (1 part by weight); pH-value: 4.5

b) bacteriological characteristics of a preparation in accordance with the invention consisting of equal parts by weight of mixture (a) and the addition product of 15 moles of ethyleneoxide to 1 mole of glycerine monooleate; pH-value 4.5

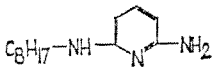
Species	Concentration of active substance in %	a) action time in minutes						b) action time in minutes					
		1	2	5	10	20	30	1	2	5	10	20	30
Staphylococcus aureus	0.1	—	—	—	—	—	—	—	—	—	—	—	—
	0.05	—	—	—	—	—	—	—	—	—	—	—	—
	0.01	—	—	—	—	—	—	—	—	—	—	—	—
	0.005	+	—	—	—	—	—	—	—	—	—	—	—
	0.001	+	+	—	—	—	—	+	+	—	—	—	—
Pseudomonas aeruginosa	0.1	—	—	—	—	—	—	—	—	—	—	—	—
	0.05	—	—	—	—	—	—	—	—	—	—	—	—
	0.01	—	—	—	—	—	—	+	—	—	—	—	—
	0.005	+	+	+	+	—	—	+	+	+	+	—	—
	0.001	+	+	+	+	+	+	+	+	+	+	+	+
Proteus vulgaris	0.1	—	—	—	—	—	—	—	—	—	—	—	—
	0.05	—	—	—	—	—	—	—	—	—	—	—	—
	0.01	—	—	—	—	—	—	—	—	—	—	—	—
	0.005	+	+	—	—	—	—	+	+	—	—	—	—
	0.001	+	+	+	+	+	+	+	+	+	+	+	+
Escherichia coli	0.1	—	—	—	—	—	—	—	—	—	—	—	—
	0.05	—	—	—	—	—	—	—	—	—	—	—	—
	0.01	—	—	—	—	—	—	—	—	—	—	—	—
	0.005	—	—	—	—	—	—	—	—	—	—	—	—
	0.001	+	+	+	—	—	—	+	+	+	+	—	—

— no bacteria growth.
+ bacteria growth

(c) Quaternary ammonium compound with 40% alkyl groups of 12 carbon atoms, 50% of alkyl groups with 14 carbon atoms and 10% alkyl groups with 16 carbon atoms (Alkylbenzyldimethyl-ammoniumchloride)

Species	Concentration of active substance in %	action time in minutes					
		1	2	5	10	20	30
Staphylococcus aureus	0.1	—	—	—	—	—	—
	0.05	—	—	—	—	—	—
	0.01	—	—	—	—	—	—
	0.005	—	—	—	—	—	—
	0.001	+	+	—	—	—	—
Pseudomonas aeruginosa	0.1	—	—	—	—	—	—
	0.05	—	—	—	—	—	—
	0.01	+	—	—	—	—	—
	0.005	+	+	+	+	+	—
	0.001	+	+	+	+	+	—
	0.001	+	+	+	+	+	+
Proteus vulgaris	0.1	+	+	—	—	—	—
	0.05	+	+	—	—	—	—
	0.01	+	+	+	—	—	—
	0.005	+	+	+	—	—	—
	0.001	+	+	+	+	+	+
Escherichia coli	0.1	—	—	—	—	—	—
	0.05	—	—	—	—	—	—
	0.01	—	—	—	—	—	—
	0.005	+	+	—	—	—	—
	0.001	+	+	+	+	+	+

(d) bacteriological effect of

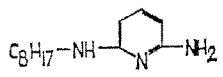


The pH-value of the 0.1% aqueous solution was adjusted with HCl to 4.5.

Species	Concentration of active substance in %	action time in minutes					
		1	2	5	10	20	30
Staphylococucs aureus	0.1	—	—	—	—	—	—
	0.05	+	—	—	—	—	—
	0.01	+	+	+	—	—	—
	0.005	+	+	+	+	+	+
Pseudomonas aeruginosa	0.1	—	—	—	—	—	—
	0.05	+	—	—	—	—	—
	0.01	+	+	—	—	—	—
	0.005	+	+	+	+	+	+
Proteus vulgaris	0.1	—	—	—	—	—	—
	0.05	+	—	—	—	—	—
	0.01	+	+	—	—	—	—
	0.005	+	+	+	+	+	+
Escherichia coli	0.1	—	—	—	—	—	—
	0.05	—	—	—	—	—	—
	0.01	+	+	—	—	—	—
	0.005	+	+	+	+	+	—

II a) *Determination of protein sensitivity*:
In contrast to the simple suspension test in which all dilutions are effected with water, the dilutions in the present test were effected with 20% aqueous solution of bovine (cattle) serum of pH-value of 5.

a') Present mixture of 1 part by weight of benzalkoniumchloride and 1 part by weight of



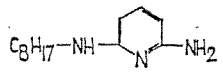
used as in Ia.

b') Benzalkoniumchloride, according to Ic; pH-value: 5

Species	Concentration of active substance in %	II a' action time in minutes 1	2	5	10	20	30	II b' action time in minutes 1	2	5	10	20	30
Staphylococcus aureus	0.1	−	−	−	−	−	−	−	−	−	−	−	−
	0.05	−	−	−	−	−	−	−	−	−	−	−	−
Pseudomonas aeruginosa	0.1	−	−	−	−	−	−	+	+	+	+	+	−
	0.05	−	−	−	−	−	−	+	+	+	+	+	+
Proteus vulgaris	0.1	+	−	−	−	−	−	+	+	−	−	−	−
	0.05	+	+	−	−	−	−	+	+	+	+	−	−
Escherichia coli	0.1	−	−	−	−	−	−	+	+	−	−	−	−
	0.05	−	−	−	−	−	−	+	+	+	−	−	−

II b) *Soap sensitivity determination:*

All dilutions were carried out with 0.1% aqueous soft soap solution.

a') Present mixture of 1 part by weight benzalkoniumchloride and 1 part by weight of  used as in Ia.

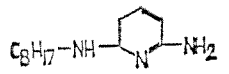
b') Benzalkoniumchloride used as in Ic.

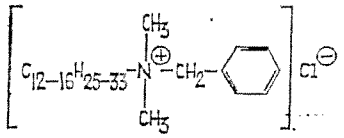
Species	Concentration of active substance in %	IIb a' action time in minutes 1	2	5	10	20	30	IIb b' action time in minutes 1	2	5	10	20	30
Staphylococcus auereus	0.1	−	−	−	−	−	−	−	−	−	−	−	−
	0.05	−	−	−	−	−	−	−	−	−	−	−	−
Pseudomonas aeruginosa	0.1	−	−	−	−	−	−	+	+	−	−	−	−
	0.05	−	−	−	−	−	−	+	+	+	+	+	+
Proteus vulgaris	0.1	+	−	−	−	−	−	+	+	+	−	−	−
	0.05	+	+	−	−	−	−	+	+	+	+	−	−
Escherichia coli	0.1	−	−	−	−	−	−	+	−	−	−	−	−
	0.05	−	−	−	−	−	−	+	+	+	+	−	−

The bacteriological superiority of the present preparations as compared with previously proposed preparations is demonstrated in the preceding tables. This superiodity applies also to a situation in which protein or anionic detergents, such as soft soap, are present.

III) Eye irritation test, according to Draize and Kelley, Drug and Cosmetic Industry, vol. 71 (1952), pages 36 to 37 and 118 to 120.

a) An aqueous solution containing 0.5% of active ingredient consisting of equal parts by weight of

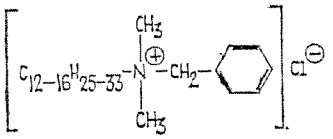




had its pH adjusted with acetic acid to a value of 4.5.

Rabbit No.		1	2	3	4	5	6	average value
1st day	A	2	3	2	2	2	2	
	B	2	2	2	2	2	2	
	C	2	2	1	2	1	2	
		6×2=12	7×2=14	5×2=10	6×2=12	5×2=10	6×2=12	11.7
2nd day	A	2	2	1	1	1	2	
	B	1	1	1	1	1	1	
	C	1	1	1	1	1	1	
		4×2=8	4×2=8	3×2=6	3×2=6	3×2=6	4×2=8	7
3rd day	A	1	1	1	1	1	1	
	B	1	1	1	0	0	1	
	C	1	1	0	0	0	0	
		3×2=6	3×2=6	2×2=4	1×2=2	1×2=2	2×2=4	4
4th day	A	1	1	0	1	0	1	
	B	0	0	1	0	0	1	
	C	0	0	0	0	0	0	
		1×2=2	1×2=2	1×2=2	1×2=2	0	2×2=4	2
7th day	A	0	0	0	0	0	0	
	B	0	0	0	0	0	0	
	C	0	0	0	0	0	0	
		0	0	0	0	0	0	0

b) As a control test, a 0.5% aqueous solution of



had its pH adjusted with acetic acid to a value of 4.5.

Rabbit No.		1	2	3	4	5	6	average value
1st day	A	3	3	3	3	3	3	
	B	2	3	2	3	3	2	
	C	2	3	2	3	3	2	
		7×2=14	9×2=18	7×2=14	9×2=18	9×2=18	7×2=14	16
2nd day	A	2	3	2	3	2	2	
	B	2	2	2	2	2	2	
	C	2	2	2	2	2	1	
		6×2=12	7×2=14	7×2×14	7×2=14	6×2=12	5×2=10	12.3
3rd day	A	1	2	1	2	1	1	
	B	1	1	1	1	1	1	
	C	1	1	1	1	1	0	
		3×2=6	4×2=8	3×2=6	4×2=8	3×2=6	2×2=4	6.3
4th day	A	1	1	1	1	1	1	
	B	1	1	1	1	1	1	
	C	0	1	0	1	1	0	
		2×2=4	3×2=6	2×2=4	3×2=6	3×2=6	2×2=4	5
7th day	A	0	1	0	1	1	0	
	B	0	0	0	0	0	0	
	C	0	0	0	0	0	0	
		0	2×1=2	0	2×1=2	2×1=2	0	1

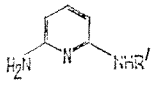
In comparing the results of test IIIa with that of IIIb, the considerably higher irritation effect of the quaternary ammonium compound as compared to that exerted by the present mixture will be recognized. The higher irritation effect is indicated by the larger numerical value of the average value.

WHAT WE CLAIM IS:—

1. A biocidal mixture, comprising

(a) a quaternary ammonium compound and

(b) a 2 - N - alkyl(or aralkyl)amino - 6-aminopyridine of the general formula

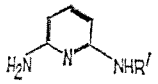


wherein R′ is an alkyl radical containing 8 to 18 carbon atoms, the number of carbon atoms being even, or a benzyl radical which is chlorinated or brominated in 2- and/or 4-position, the weight ratio of (a):(b) being from 1:5 to 5:1.

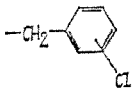
2. A mixture as claimed in Claim 1, wherein the mixture also comprises:—

(c) a non-ionic tenside, the weight ratio of (a):(b):(c) being 1:5:10 to 5:1:0.1.

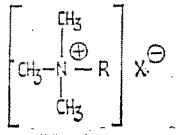
3. A mixture as claimed in Claim 1 or 2, wherein said component (b) is a compound of the general formula



wherein R′ is an alkyl radical containing 8 to 2 carbon atoms or a radical of the formula

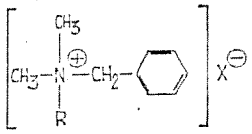


4. A mixture as claimed in any one of Claims 1 to 3, wherein said component (a) is a compound of the general formula



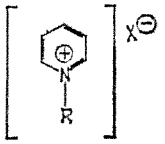
wherein R is an even-numbered straight-chain alkyl radical containing 8 to 18 carbon atoms and X is a halogen atom, or an OH or CH_3OSO_3 group.

5. A mixture as claimed in any one of Claims 1 to 3, wherein the component (a) is a compound of the general formula



wherein R is an even-numbered straight-chain alkyl radical containing 8 to 18 carbon atoms and X is a halogen atom, or an OH or CH_3OSO_3 group.

6. A mixture as claimed in any one of Claims 1 to 3, wherein said component (a) is a compound of the general formula



wherein R is an even-numbered straight-chain alkyl radical containing 8 to 18 carbon atoms and X is a halogen atom, or an OH or CH_3OSO_3 group.

7. A biocidal mixture in accordance with Claim 1 substantially as hereinbefore described in any one of the foregoing Examples.

8. A biocidal preparation containing, as its active ingredient, a mixture as claimed in any preceding claim and an inert carrier.

9. A preparation as claimed in Claim 8, wherein said inert carrier is water, an alcohol or glycolether.

10. A preparation as claimed in Claim 8 or 9, wherein the pH of the preparation does not exceed a value of 9.

11. A preparation as claimed in any one of Claims 8 to 10, wherein the concentration of the active ingredient is from 0.001 to 0.1 percent by weight.

12. A biocidal preparation in accordance with Claim 8 substantially as hereinbefore described in any one of the foregoing Examples.

TREGEAR, THIEMANN & BLEACH,
Chartered Patent Agents,
Melbourne House, Aldwych,
London, W.C.2.
Agents for the Applicants.

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